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Caenorhabditis Elegans as a Model for the Study of the Toxicity of Organophosphate Insecticides- A Minireview

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A B S T R A C T

When one proposes to embark on the journey of toxicological evaluations, the most important consideration becomes the choice of an appropriate study model. The scientific community is increasingly paying attention to alternative models for toxicological evaluations in view of ethical considerations, requirement of a large number of animals and longer life cycles of higher mammalian models. In vitro applications such as cell suspensions, tissue slices, primary cell cultures and cell lines definitely offer the advantage of simplicity and rapidity with which they can be employed for mechanistic studies. However, they fail in offering in vivo like complexity with respect to behavior, physiology and biochemistry and neurochemical networking. In an endeavor to enjoy these advantages, researchers world over are increasingly opting for non-mammalian alternative models for toxicity evaluations. This minireview intends to provide an account of utility of Caenorhabditis elegans as a model for studying the toxicity of organophosphate compounds.

Keywords: Caenorhabditis elegans, organophosphate compounds, toxicity studies.

1. INTRODUCTION

Organophosphate compounds (OP) are a highly toxic class of chemicals that are intentionally used for the purpose of pest control. Organophosphate toxicity is one of huge concern due to potential for occupational and intentional exposure. OP compounds act mainly by causing inhibition of the enzyme, acetylcholinesterase (AChE). Neurotoxicity due to cholinergic stress is the characteristic clinical outcome associated with OP compounds [1]–[3]. Additionally experimental and human studies show that these compounds have propensity to alter glucose homeostasis and interfere with hepatic and adipose tissue homeostasis [4]–[7].

Perhaps, the most utilized non-mammalian models in toxicological evaluations are Caenorhabditis elegans, Drosophila and Zebra fish. However, in the recent past its C. elegans that has emerged as the most preferred alternative toxicology model. Indeed, C. elegans finds application as a model for studies related to larger variety of biological processes. The introduction of C. elegans was made by Sydney Brenner in the second half of the twentieth century to study development and neurobiology [8]. Several fundamental features of C. elegans such as that make it a very reliable model are listed in **Table 1**[9]–[12].

Table 1. Unique features of *Caenorhabditis elegans*

Features	**Advantages**
Inexpensive and easy to culture, small size (1 mm)	Can be adopted for research by even low-funded laboratories, Suitable for and highthrougput methods
Short life cycle (3 days at 20^{o}C) and life span (3-4 weeks)	Rapid assessments and multigenerational studies
Completely sequenced genome	Allows deeper understanding at genetic level
Transparent body	Allows cellular visualization; useful in assessments involving chromogenic and fluorescence reporter genes
Hermaphrodite	'true breeding type'

2. LITERATURE REVIEW

Role of acetylcholinesterase system is well established in the worm [13]. Cholinergic system is important for processes like egg laying, locomotory and feeding behaviors in the worm [14]–[16], and hence worm is adequate is offering several behavioral endpoints for study of toxicity of OP compounds. Therefore it is not surprising that the worm has been extensively used in studying various aspects of OP toxicity such as neurotoxicity, behavioral toxicity, oxidative stress, impact on gene expression. Further, C. elegans offers valuable end points such as pharyngeal pumping and

paralysis, which could be used as simple tools for screening of oxime-based AChE reactivators, which are important life saving antidotes for OP toxicity. **Table 2** lists important studies conducted with Caenorhabditis elegans as a model for studying the above said aberrations associated with OP compounds.

Table 2: Studies employing *Caenorhabditis elegans* as a model for study of organophosphate toxicity

	Summary of the study and reference
1	Fifteen organophosphate compounds were studied for their toxicity and behavioral effects. Order of toxicities of selected compounds was found to correlate with their rodent toxicities. Behavioral toxicities observed was fund to correlate well with inhibition of AChE[17].
2	Chlorpyrifos exposure was associated with AChE inhibition, developmental impairments and up regulation of hsp16-2 (proteotoxicity response), metalothionein-2 and cep-1 (p53 like protein) [18].
3	Comparative assessment of toxicity of 10 organophosphate compounds to *C. elegans* was performed using lethality, AChE activity and movement behaviour as end points. All tested compounds were associated with lethality, AChE inhibition and impairments in movement. A significant correlation was found between median lethal concentrations of pesticides and their median lethal doses in rodent system from literature [19].
4	Toxicity of dichlorvos was studied for its toxicity to *C. elegans* for different periods of exposure. Prolonged periods of exposure dramatically increased the toxicity of dichlorvos to *C. elegans*. Exposure for short period of time (4h) was sufficient to elicit severe AChE inhibition, while prolonged exposure was (greater than 12h) was found to be associated with heat shock response in the transgenic PC27 strain [20].
5	Sub-lethal concentration of dichlorvos was associated with AChE inhibition, paralysis, nose-contraction, inhibition of pharyngeal pumping feeding inhibition and inhibition of egg laying in *C. elegans*[21].
6	Impact of 72h-exposure to chlorpyrifos, diazinon and a mixture of the two was studied on gene expression in *C. elegans*. As result of exposure, transcriptional responses were obtained in the domains of genes involved in stress, detoxification, innate immunity, and transport and metabolism of lipids [22].
7	Monocrotophos was reported to cause parkinsonism changes in *C. elegans* in a manner similar to the chemical model of Parkinson disease, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Monocrotophos was found to cause locomotory defect and decrease in dopamine content. In addition, dopaminergic neurodegeneration was observed in a transgenic strain treated with monocrotophos[23].
8	Dichlorvos was found to be more potent than chlorpyrifos in causing impairments in feeding behaviour in *C. elegans*. Further, dichlorvos induced more pronounced up regulation of genes (studied in GFP-reporter strains) involved in proteotoxicity responses, xenobiotics handling systems, antioxidant system and core-stress responsive genes. Cyp-34A9 was up regulated in worms exposed to both dichlorvos and chlorpyrifos [24].
9	Toxicity of monocrotophos to *C. elegans* was determined using 4h exposure system. At sub lethal concentrations, the OP compound was associated with suppression of AChE and carboxylesterase activity, along with paralysis and reduced brood size [25].
10	Chlorpyrifos elicited alpha-synuclein aggregation along with reduced lipid content in a transgenic strain of *C. elegans*[26].
11	Monocrotophos was found to cause severe paralysis and AChE inhibition at sub-lethal concentrations. Paralysis induced by monocrotophos at sub lethal concentrations was prevented by co-treatment with pralidoxime, which is antidote for OP toxicity [27]
12	Treatment of the worms with quinalphos was associated with impairments in feeding, body-bending and head-trashing behaviors. Further, the pesticide led to up regulation of *daf-16* and *glod-4*, while stress-responsible genes such as *daf-2* and *age-1* were down regulated along with genes involved in locomotion (*unc-47* and *unc-13*) [24].
13	Toxicity and anti-cholinesterase potential of monocrotophos was compared with that of acephate. Monocrotophos was more toxic to *C. elegans* in a 4h-exposure test. Further, at sub lethal doses of toxicological equivalence, monocrotophos was found to cause stronger inhibition of AChE[28] than acephate.
14	Products of photolysis of chlorpyrifos induced by 1h-exposure to simulated sunlight have been reported to exert more toxicity to cholinergic and GABAeric neurons in *C. elegans* as compared to the effect of unexposed chlorpyrifos [29].
15	AChE-inhibition dependence was studied on inhibition of pharyngeal pumping in C. elegans, in addition to the effect of AChE an activating oxime on above said parameters. Pharyngeal pumping was improved by pralidoxime in worms treated with paraxon-ethyl. Data from this paper suggests that pharyngeal pumping could be used as an *in vivo* tool for screening efficacy of AChE reactivators [30].

3. CONCLUSIONS

With a short life sapn and life cycle, well-conserved cholinergeic system, *C. elegans* is a very useful model for studying toxocity of organophosphates. The nematode is of great use for evaluation of mechanisnistic aspects of OPI toxicity, as well as for screening of cholinesterase reactivators and antidotes for OPI toxicty.

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